

7341.002

Inspection of Tissue Establishments

Upon Receipt

September 30, 2004

57J--01 thru 57J--06  
57K--01 thru 57K--03  
57L--01 thru 57L--02  
57M--01 thru 57M--02  
57O--01 thru 57O--02  
and 57P--99

41002

This compliance program is effective upon receipt.

#### FIELD REPORTING REQUIREMENTS

A copy of each establishment inspection report (EIR), the endorsement and FDA-483 should be routinely submitted preferably by electronic means to: [cberinspections@cber.fda.gov](mailto:cberinspections@cber.fda.gov).

- If electronic submission is not feasible, forward a copy of each EIR, the endorsement and FDA-483 to CBER, Office of Compliance and Biologics Quality (OCBQ), to the attention of the Division of Inspections and Surveillance (HFM-650), at the mailing address listed below.

Recommendations for administrative or regulatory action should be sent to the attention of CBER/OCBQ/Division of Case Management (HFM-610), at the following address.

Food and Drug Administration  
Center for Biologics Evaluation and Research  
Office of Compliance and Biologics Quality  
1401 Rockville Pike  
Rockville, MD 20852-1448

Note: There are specific reporting requirements in Part III.A.1.

**PROCESS PROFILE REPORTING**

Do not profile tissue banks and eye banks that are regulated solely under Sec.361 of the PHS Act and 21 CFR 1270 and subparts A and B of Part 1271, and that are involved in the recovery, processing, testing, screening, storage, and distribution of human tissues by methods that do not change tissue function or characteristics.

**NOTE:** This Compliance Program does not cover human tissues that are regulated as devices (e.g. heart valves and dura mater), but for purposes of clarification, the “device” tissues are profiled, just like any other finished device.

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#### **ATTACHMENT A**

CMS CONTACTS

#### **ATTACHMENT B**

REGULATION OF HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED  
PRODUCTS (revised May 2002)

#### **ATTACHMENT C**

TISSUE REFERENCE GROUP

## **PART I - BACKGROUND**

The regulation of human tissue intended for transplantation (human tissue) is accomplished under the legal authority of Section 361 (Sec. 361) of the Public Health Service Act (PHS Act) [42 USC 264]. This section authorizes the Surgeon General, with the approval of the Secretary, Department of Health and Human Services, to make and enforce such regulations as judged necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the United States or from State to State. Section 361 of the PHS Act focuses on preventing the introduction, transmission, and spread of communicable diseases.

In the early 1990's, the Centers for Disease Control and Prevention (CDC) reported that human immunodeficiency virus (HIV) had been transmitted through transplantation of human tissue. Information was also reported which suggested that potentially unsafe tissue was being imported into the United States for transplantation into humans. Prompted by reports that potentially unsafe bone was being imported, the Commissioner of Food and Drugs ordered an immediate investigation. Information resulting from this investigation identified an immediate need to protect the public health from the transmission of HIV and hepatitis B and C through transplantation of unsuitable tissue. Concerns that disease transmission could occur coupled with information derived from these investigations prompted the Food and Drug Administration (FDA, the Agency) to publish an interim rule in December 1993 that specifically required certain communicable disease testing, donor screening, and recordkeeping for human tissue intended for transplantation.

In the Federal Register (FR) of July 29, 1997 (62 FR 40429), FDA issued the final rule on human tissue intended for transplantation to clarify and modify many of the provisions of the December 14, 1993, interim rule. The final rule, codified as 21 CFR 1270, became effective January 26, 1998, and applies to human tissue procured on or after that effective date. For tissues procured prior to January 26, 1998, the provisions of the interim rule apply. Since FDA chose to regulate tissues under Section 361 of the PHS Act, the provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act) are not applicable to tissues regulated under 21 CFR 1270.

In 1997, the agency announced its plans for human cells, tissues, and cellular and tissue-based products in two documents: "A Proposed Approach to the Regulation of Cellular and Tissue-Based Products" (62 FR 9721, March 4, 1997) and "Reinventing the Regulation of Human Tissue". The proposed approach described a comprehensive plan for regulating human cells, tissues, and cellular and tissue-based products that would include establishment registration and product listing, donor-suitability requirements, good tissue practice regulations and other requirements. Under this tiered, risk-based approach, we proposed to exert only the type of government regulation necessary to protect the public health. To accomplish this goal, we planned to issue new regulations under the communicable disease

provisions of the PHS Act. Some human cellular and tissue-based products would be regulated only under these new regulations, while other human cellular and tissue-based products would also be regulated as drugs, devices, and/or biological drugs. FDA requested written comments on the proposed approach and, on March 17, 1997, held a public meeting.

Since 1997, the Agency has published three proposed rules to implement the proposed approach. They are:

- “Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products” (1999, the “registration proposed rule”). The rule proposed to require cell and tissue establishments to register with FDA and to submit a list of their human cellular and tissue-based products to FDA. FDA also proposed modifications to current registration and listing requirements for drugs and devices under which cell and tissue establishments already regulated under the FD&C Act and/or section 351 of the PHS Act (42 U.S.C. 262) would register and list following the new procedures.
- “Suitability Determination for Donors of Human Cellular and Tissue-Based Products” (1999, the “donor suitability proposed rule”), and
- “Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement” (2001, the “GTP proposed rule”).

Together, these three rules when finalized would establish a comprehensive regulatory program for human cellular and tissue-based products, to be contained in Part 1271 (21 CFR Part 1271).

FDA had intended to finalize the registration proposed rule with the other rules that would make up Part 1271 in its entirety, and to implement all three rules together. However, concerns about the safety of tissue led FDA to believe that accelerating the collection of basic information about the rapidly growing tissue industry is vital. Representatives of key tissue-related organizations also supported finalization of this regulation as quickly as possible, instead of awaiting simultaneous publication with the other tissue regulations. Therefore, FDA decided to make the registration rule final with staggered effective dates, while continuing to develop the remainder of the final rules that will complete Part 1271.

On January 19, 2001, FDA issued the final rule to establish a unified registration and listing program for human cells, tissue, and cellular and tissue-based products (HCT/P’s). Establishments that engage in the recovery, screening, testing, processing, storage, or distribution of human tissue intended for transplantation regulated on that date under section 361 of the PHS Act and the regulations in Part 1270 were required to register with FDA and list their HCT/P’s by April 4, 2001 [as described in Parts 1270.3(j) and 1271.3(d)(1)]. The effective date for all other human cells, tissues, and cellular and tissue-based products [as described in 1271.3(d)(2)] was originally scheduled to be January 21, 2003. However, unanticipated delays in completing the rulemaking for the remainder of part 1271 resulted in the effective date being extended to January 21, 2004.

Once the entire rulemaking is complete, the new regulatory approach would apply to a broad range of human cells, tissues, and cellular and tissue-based products, including reproductive cells and tissue; hematopoietic stem cells; and tissues and cells regulated as devices, drugs and/or biological products.

The proposed regulation anticipates that the new Part 1271 will be made up of six subparts:

- A - general provisions pertaining to the scope and applicability of Part 1271, as well as definitions.
- B - registration and listing procedures.
- C - provisions for donor-suitability.
- D - current Good Tissue Manufacturing Practice (CGTP) requirements.
- E - labeling and reporting requirements.
- F - inspection and enforcement provisions.

**NOTE:** Subparts E and F are applicable only to those HCT/P's regulated solely under section 361 of the PHS Act.

Section 1271.10, in subpart A, sets out the criteria that form the foundation of our tiered, risk-based approach to regulating HCT/P's. HCT/P's that meet all of these criteria are subject only to regulation under section 361 of the PHS Act. When all the rules that will make up Part 1271 become effective, these HCT/P's will be subject to the regulations in Part 1271, and no premarket submissions would be required. HCT/P's that do not meet the criteria for regulation as "361" HCT/P's will be regulated as drugs, devices, and/or biological products.

## **PART II - IMPLEMENTATION**

This program provides information about compliance and surveillance activities relating to human tissue intended for transplantation (human tissue). The establishments covered by the program are subject to inspection by FDA to determine compliance with the applicable provisions of Title 21, Code of Federal Regulations, Part 1270, and subparts A and B of Part 1271.

**NOTE:** *Human tissue*, as defined in 21 CFR 1270.3(j), is the term used to identify products covered by this Compliance Program. The registration and listing final rule that became effective April 4, 2001, is only currently applicable to the human cells, tissues, or cellular or tissue-based products (HCT/P's) that are referenced in 1271.3(d)(1).

### **A. OBJECTIVES**

The objective in issuing this program is to assure that (a) all human tissue subject to 21 CFR 1270 and subparts A and B of Part 1271 is recovered, processed, stored and/or distributed under conditions designed to prevent transmission of communicable disease, and (b) each donor was adequately screened and tested. This is accomplished by:

1. Providing guidance to investigators conducting inspections of tissue establishments;
2. Identifying establishments that are not operating in compliance with the applicable regulations and encouraging voluntary compliance;
3. Providing regulatory and administrative guidance to compliance officers;
4. Establishing an inventory of establishments active in the tissue industry.

### **B. PROGRAM MANAGEMENT INSTRUCTIONS**

1. Human tissues that fall within the scope of 21 CFR 1270 and subparts A and B of Part 1271, and are therefore covered by this compliance program include:
  - Bone (including demineralized bone) **NOTE:** demineralized bone combined with handling agents such as glycerol, gelatin, collagen, etc., is regulated as a medical device and is *not* covered by this compliance program.
  - Ligaments
  - Tendons
  - Fascia
  - Cartilage
  - Ocular Tissue (Corneas and Sclera)
  - Skin
  - Arteries and Veins (except umbilical cord veins)



Pericardium  
Amniotic membrane

**NOTE:** Each of the above products is covered solely by 21 CFR 1270 and subparts A and B of Part 1271, if it is:

- 1) minimally manipulated;
- 2) intended for a homologous use only as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;
- 3) not combined with a drug or device, except for a sterilizing, preserving, or storage agent; **and**
- 4) either:
  - (i) does not have a systemic effect and is not dependent upon the metabolic activity of living cells for the primary function; or
  - (ii) has a systemic effect or is dependent upon the metabolic activity of other cells for the primary function, and: (a) is for autologous use; (b) is for allogenic use in a first- or second-degree relative; or (c) is for reproductive use.

2. Human tissues that are NOT regulated under 21 CFR 1270 and subparts A and B of Part 1271, and NOT covered by this compliance program include:

Whole vascularized organs for transplantation (kidneys, lungs, heart, liver, pancreas)  
Semen and other reproductive tissue  
Human Milk  
Tissue for autologous use only  
Bone Marrow

3. Some human tissues that are NOT regulated under 21 CFR 1270 and subparts A and B of Part 1271 were regulated by FDA prior to the implementation of the interim rule and are still currently regulated as drugs, biological products, or medical devices. These products are NOT covered by this compliance program and include:

Blood and blood products  
Heart valves  
Corneal lenticules  
Umbilical cord veins  
Interactive wound dressings  
Dura mater  
Cultured skin

During inspections, multiple products may be encountered and each must be considered as to the proper regulation to apply. If it is unclear how the product is regulated because of the way it is processed or manipulated, the Division of Inspections and Surveillance (HFM-650) should be contacted for clarification or guidance. Investigators should be prepared to provide details regarding the method of processing and the content of the labeling and promotional materials associated with the product to facilitate the decision-making process. Attachment B is intended to assist Investigators and Compliance Officers in determining which regulations to apply to which products.

4. Tissue products covered by other compliance programs:

- Blood and blood products are covered under CP 7342.001 - “Inspection of Licensed and Unlicensed Blood Banks, Brokers, Reference Laboratories, and Contractors”; and CP 7342.002 - “Inspection of Source Plasma Establishments”
- Plasma derivatives - CP 7342.006 - “Inspection of Plasma Derivatives of Human Origin”
- Human tissues regulated as medical devices(e.g., heart valves, dura mater, cultured skin) - CP 7382.845 - “Inspection of Medical Device Manufacturers”
- Autologous, allogeneic, or xenogeneic cells whose biological characteristics have been altered (propagated, pharmacologically treated, etc.) *ex vivo* and gene therapy products are regulated as biologic drugs - CP 7341.001 - “Inspection of Licensed Therapeutic Drug Processors”

5. Establishment registration, listing, and inspection status:

- All establishments engaged in the recovery (or procurement), processing, storage and/or distribution of human tissue as defined in 21 CFR 1270.3(j) and 1271.3(d)(1), and in screening and testing of the donor had to register with and submit to FDA by April 4, 2001, a list of each human tissue product manufactured as defined in 1271.3(e).  
**NOTE:** These establishments include not only tissue banks (including specialty banks such as eye banks or skin banks) and tissue processors, but also other types of establishments including hospitals, clinics, testing laboratories, medical examiners or coroners offices, brokers that take possession of tissue, or other facilities that may be engaged in one or more of the functions mentioned above unless they are excepted by 1271.15.
- New establishments have to register and list within 5 days of beginning operations.

- Manufacturers of all other HCT/P's as defined in 1271.3(d)(2) were to begin registering with the FDA and listing their HCT/P's on January 21, 2003. However, because rulemaking proceedings have been delayed, FDA is extending the effective date for requiring registration of the HCT/P's as described in 1271.3(d)(2) to January 21, 2004.
- The establishment that initiates the tissue procurement is responsible for registering with FDA and would be routinely inspected. This may not necessarily be the physical location where the procurement takes place. For example, if a procurement firm dispatches a team to a funeral home or hospital morgue to procure tissues from a donor, we would *not* routinely inspect the funeral home or the morgue if they solely function as the site of procurement. However, if the funeral home or hospital is engaged in any of the activities outlined in 1271.3(e), then that would prompt registration and routine FDA inspection.
- Hospitals and transplanting institutions that store and dispense tissue only for their own use are considered end users and are NOT subject to ROUTINE inspection. However, should the Agency determine that violative tissue is in the user's custody, FDA is not precluded from inspecting them or issuing the firm an order for retention, recall or destruction.
- CBER maintains an alphabetic listing of currently registered tissue establishments that is accessible on their web site at <http://www.fda.gov/cber/tissue/hctregistabl.htm>. Questions pertaining to tissue establishment registration or product listing should be directed to the CBER Tissue Registration Monitor, HFM-770 (see CBER contacts in Part VI).

## 6. Frequency of inspection

There is currently no statutory requirement for FDA to conduct routine biennial inspections of human tissue intended for transplantation. Each district should decide which firm(s) to inspect based on the resources they have been allotted in the ORA workplan, and the risk-based selection priorities listed below:

- (1) Firms whose last inspection was classified OAI.
- (2) Firms for which FDA has received surveillance information indicating there is a potential violation of 21 CFR 1270 and subparts A and B of Part 1271.
- (3) Firms which FDA has never inspected and which are known to lack accreditation by a standard setting organization such as the American Association of Tissue Banks (AATB) or the Eye Bank Association of America (EBAA).
- (4) Firms which FDA has never inspected and which are known to be accredited.
- (5) Laboratories that perform required viral marker testing for tissue banks.
- (6) All other human tissue establishments.

## 7. Biosafety issues

IOM Section 145 addresses precautions FDA employees should adopt for their own protection. Investigators should be cautious and take suitable precautions to prevent infection in tissue banks or other places where they may be subject to contact with infectious substances. Body tissues should be considered potentially infectious and capable of transmitting disease, including HIV and hepatitis.

## 8. Inspection forms

At the beginning of each inspection, a Form FDA-482 should be issued to the most responsible individual available at the tissue establishment. The Notice of Inspection is not being given pursuant to section 704 of the Food, Drug, and Cosmetic Act. Issuance of a written notice is not required by section 361 of the PHS Act, however, the agency has decided that it is reasonable and customary to issue an FDA-482 prior to initiating an FDA inspection of a tissue establishment. The FDA-482 references Section 361, Part G, of the PHS Act. At the close of the inspection, observations focusing on the requirements of 21 CFR 1270 and subparts A and B of Part 1271, should be listed on a Form FDA-483 and issued to the most responsible individual.

### **PART III - INSPECTIONAL**

#### **A. OPERATIONS**

##### **1. General**

- a. Since the tissue regulations were promulgated under Section 361 of the PHS Act, inspections of human tissue establishments must focus on the transmission of communicable disease.

If, during the inspection, the investigator encounters what are believed to be serious violations, the District should alert the CBER/OCBQ/Division of Case Management.

- b. In order to gain a full understanding of the operations of the tissue establishment:
- (1) Determine which functions are performed by the establishment, e.g., recovery, screening, testing, processing, storage, and distribution, and which functions are performed at other locations or by other firms under contract.
  - (2) Determine the type(s) of tissues recovered, processed, stored and/or distributed by the establishment and if the establishments' human tissues meet the definition in 21 CFR 1270.3(j).
  - (3) Determine whether the establishment has registered with FDA and listed its human tissues as required by 21 CFR 1271.
  - (4) Determine if the establishment has received foreign tissue or if they have received solicitations to purchase foreign tissue. If so, notify ORO/DFI program contact by e-mail or telephone, so that the foreign firms can be added to the international OEI.
  - (5) Determine if the tissue bank participates in an established network of firms or in cooperation with other establishments in the procurement of tissue.  
**NOTE:** Regarding the firms that perform activities covered by 21 CFR 1270 and subparts A and B of Part 1271, determine whether they are in the OEI, and if not, notify the home district.
  - (6) Determine the number of donors per year from whom the firm procures and/or processes tissues.

- (7) Determine what human tissues are in inventory, both in quarantine and those identified as suitable for transplantation.
- (8) Determine if the establishment is a member of, or applying for membership in, any accrediting organization (e.g., AATB, EBAA) and whether it is accredited or if it has been accredited in the past.
- (9) Determine the procedures and practices for the disposition of human tissue identified as unsuitable for transplantation.
- (10) Compare the firm's actual practices with their written SOPs for all operations involving procurement, donor screening, donor testing, tissue processing, storage and distribution.

## 2. Donor Testing

- a. Infectious disease testing is a required element in the suitability determination of donors of human tissue intended for transplantation. All donors must be tested and found negative using FDA licensed screening tests for the following communicable viruses: HIV-1/2, hepatitis B, and hepatitis C.

FDA licensed screening tests labeled for cadaveric specimens must be used when available (unless the specimen being tested is a pre-mortem specimen). FDA has two licensed screening tests that have been approved and are specifically labeled for use with cadaveric serum specimens: Genetic Systems HBsAg EIA 2.0 and Genetic Systems HIV-1/HIV-2 Peptide EIA. FDA licensed HIV and hepatitis tests are listed on the FDA website at <http://www.fda.gov/cber/products/testkits.htm>. When additional test kits are approved for use on cadaveric specimens, their names will also be posted on this site.

To address the implementation of these new tests, CBER developed a document, "Guidance for Industry: Availability of Licensed Donor Screening Tests Labeled for Use with Cadaveric Blood Specimens", dated June 2000, and posted on CBER's External web site at <http://www.fda.gov/cber/guidelines.htm>. These new tests should be implemented as soon as feasible, but no later than January 31, 2001. **NOTE:** It is NOT necessary for firms to retest cadaveric specimens from donors who have already been tested prior to the implementation date.

- b. Repeatedly reactive screening test results for any of the viral markers required by 21 CFR 1270 indicate that the donor may have been exposed to and/or be infected with the particular virus. The final rule [1270.21(a)] specifically identifies “screening” as the type of test required. Therefore, tissue that is repeatedly reactive in a screening test is not suitable for use even if confirmatory tests are negative.
- c. A tissue establishment that performs donor suitability determinations is required to have and follow standard operating procedures for testing. The SOPs should include written procedures for all significant steps in the infectious disease testing process. One of these steps is the collection, identification, handling and shipping of donor test specimens.

Our expectation is that the firm will use the best quality specimen that can be obtained for infectious disease testing. A pre-mortem specimen that has been properly handled is usually a good quality sample. If the patient was transfused, a pre-transfusion sample is preferred because it eliminates the concerns regarding plasma dilution. However, in many cases, the tissue establishment has no choice except to perform infectious disease testing using cadaveric serum specimens that may be hemolyzed, because there is no other specimen available. **NOTE:** Hemolyzed specimens may be used, however, the first test result obtained must be considered the test of record regardless of the outcome.

If the tissue bank that determines donor suitability contracts out the required testing to an outside laboratory, then the bank must have assurance that the laboratory is conducting the testing in accordance with 21 CFR 1270. The bank has the flexibility to determine the best method for achieving that assurance. Auditing the testing firm periodically is acceptable, as well as obtaining a written guarantee that the lab is complying with 21 CFR 1270.

- d. Human tissue from a donor whose blood specimen may have been diluted sufficiently by transfusions/infusions to affect infectious disease test results is unsuitable unless the specimen has been assessed and deemed acceptable using an established procedure to calculate plasma dilution, i.e., an algorithm.

If a pre-transfusion/infusion specimen is unavailable for testing, then for the tissue to be assessed for suitability, a post-transfusion specimen must be assessed for plasma dilution using an algorithm prior to testing. Factors regarding the selection of an appropriate algorithm for determining plasma dilution are discussed in the July 1997 “Guidance for

Screening and Testing of Donors of Human Tissue Intended for Transplantation”  
<http://www.fda.gov/cber/guidelines.htm>.

The following criteria should be considered in evaluating the need for using an algorithm to determine if plasma dilution may affect infectious disease test results:

- (1) the tissue donor was transfused or infused and an adequate pre-transfusion/infusion specimen is not available for infectious disease testing;
- (2) in adult donors (greater than 12 years of age), if blood loss is known or suspected to have occurred;
- (3) if preceding the collection of the donor specimen in adult donors, more than 2,000 milliliters of whole blood, reconstituted blood, red blood cells, and/or colloids have been administered within the previous 48 hours; or 2,000 ml. of crystalloids have been administered within the previous one hour; or any combination of these has occurred;
- (4) if preceding the collection of the donor specimen in a donor who is 12 years of age or less, any amount of fluids have been transfused/infused within the previous 48 hours.

If the above criteria have been met, the tissue is considered unsuitable until an algorithm defined in the tissue establishment’s SOPs is used to assess whether the administered fluids affected the test results. If the dilution is calculated to be sufficient enough to affect the test results, then the tissue is deemed unsuitable. The July 1997 “Guidance for Industry: Screening and Testing of Donors of Human Tissue Intended for Transplantation” lists a Plasma Dilution and Testing Algorithm which FDA considers acceptable to meet the requirements of 21 CFR 1270.

If a firm’s plasma dilution algorithm is suspected of being inadequate, collect a copy of it and the applicable SOP, and fax them to HFM-650 (see Part VI for the fax number). CBER will attempt to provide comments by the close of the inspection.

- e. Many tissue establishments contract the services of an outside testing laboratory to perform the required screening tests. To the extent possible, the investigator should determine from the tissue bank how the testing is conducted. The tissue establishment must assure that the infectious disease testing is performed by a laboratory registered with FDA and appropriately certified by the Centers for Medicare and Medicaid Services (CMS), formerly HCFA, under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). The tissue establishment must also assure that the laboratory is operating in compliance with 21 CFR 1270. This includes assurance that any required test being conducted to determine the suitability of a donor is performed using an FDA licensed screening test appropriate for cadaveric specimens, if available, and is conducted in accordance with the manufacturer’s instructions for use.



Laboratories that perform testing to determine donor suitability are subject to FDA inspection. The testing laboratory must retain records of all original test results and the interpretation of the results. Copies of the interpretation of the test results should also be provided to, and retained by, the person or establishment making the final determination of donor suitability.

In the EIR, report what laboratory(ies) are performing the required testing and whether or not the facilities are CLIA certified and FDA registered. If any of these laboratories are not in your district, notify the home district(s) to determine if they are aware that these laboratories are doing required testing for tissue establishments. Inspectional follow-up may be required.

- The CLIA certification status of a laboratory can usually be determined at the firm. If you have a question about whether or not the laboratory is actually CLIA certified, contact the CMS regional contact person for your district (see Attachment A).
  - CLIA certified laboratories are surveyed by either CMS or an accrediting organization authorized by CMS to survey laboratories (“deemed status”), or are located in a State approved for exemption under CLIA. CMS issues a certificate of compliance to laboratories surveyed by its inspectors and found to be “in compliance”. Laboratories inspected by a CMS deemed status organization (e.g., JCAHO, CAP, AABB, AOA) are awarded a certificate of accreditation by that organization.
- f. According to 21 CFR 1270.21(d), human tissue for transplantation shall be accompanied by records indicating that the donor's specimen has been tested and found negative using FDA licensed screening tests for HIV-1/2, hepatitis B and hepatitis C viruses, and that licensed screening tests labeled for cadaveric specimens must be used when available. The results of all tests and retests must be maintained and available for review during an inspection. For additional information regarding viral marker testing refer to the July 1997 “Guidance For Industry: Screening and Testing of Donors of Human Tissue Intended For Transplantation”.
- All tissue recovered from a donor who tests repeatedly reactive by a licensed screening test relative to HIV or hepatitis is considered unsuitable for transplantation and must be quarantined until appropriate disposition occurs regardless of the results of supplemental testing.
  - Under no circumstances shall unsuitable tissue be used for transplantation in humans.

- g. If more than one tissue establishment tests a sample from a donor, and any one of those establishments becomes aware of indeterminate, repeatedly reactive, or positive test results relative to HIV, hepatitis B or hepatitis C, *even if the tests are not specifically required by the final rule*, the tissue from that donor is considered not suitable for transplantation. However, a donor who only tests repeatedly reactive for anti-HBs would **not** be considered unsuitable provided that all other donor suitability requirements are met.

It is not uncommon to have multiple procurers of tissues (as well as organs) from the same donor, and in cases where procurers test the donor independently of each other, there exists the possibility that their laboratory results may not be in agreement. Each tissue establishment should have an SOP for addressing discordant test results. FDA recommends that a tissue establishment notify all known procurers of any information that would render a donor unsuitable.

An investigator who encounters a situation involving discordant test results should determine and report what procurers are involved, if they were made aware of the repeatedly reactive, indeterminate or positive test results relative to HIV, hepatitis B, or hepatitis C, and if available, what action the procurers took in response to the notification. If deemed necessary, CBER will be responsible for notifying other federal agencies.

### 3. Donor Screening

- a. Donor screening is also critical in determining the suitability of an individual to donate human tissue for transplantation. Donor screening shall include determining the donor's identity and review of the donor's relevant medical records to assure freedom from risk factors for and clinical evidence of hepatitis B, hepatitis C, and HIV. The relevant medical records means a collection of documents including a donor medical history interview, a physical assessment of the donor, laboratory test results, medical records, existing coroner and autopsy reports, and any other available information or documents (e.g., police reports), which may help establish the suitability of an individual to donate tissue.
- b. The donor screening SOP should include written procedures for all significant steps in the obtaining, reviewing, and assessing of the relevant medical records of a prospective donor.
- c. FDA considers the donor medical history interview to be a documented dialogue with an individual or individuals who would be knowledgeable of the donor's relevant medical history and social behavior, such as the donor, if living, the next of kin, the nearest available relative, a member of the donor's household, an individual with an affinity relationship, and/or the primary treating physician. It is preferable that these interviews

take place in person, however, telephone interviews are also acceptable.

- d. In assessing donor suitability, it is essential that information regarding the donor's potential risk of exposure to HIV and hepatitis be elicited, documented and considered in accordance with the firm's SOPs. The standard industry practice is to employ a donor medical history questionnaire to conduct and document the donor medical history interview. The questionnaire should be reviewed to ensure that its evaluation of the donor's suitability is consistent with the requirements in 21 CFR 1270.21(f-g).

If investigators encounter a firm that relies on electronic audio methods such as cassette tapes or compact discs to record the donor medical history interviews of the next of kin or other knowledgeable individuals, FDA has access to those recordings under 1270.33(f) and may copy those recordings under 21 CFR 1270.41(d). Every effort should be made during an inspection to compare some electronic audio records to the corresponding transcribed/written donor medical/social history questionnaire to determine if the information transcribed was an accurate reflection of what was electronically recorded.

The FDA's "Guidance for Industry: Screening and Testing of Donors of Human Tissue Intended for Transplantation" dated July 1997 provides recommendations regarding what factors should be included in the donor medical history interview.

Information regarding a donor's behavior may reveal specific conduct consistent with an increased risk of exposure to HIV and hepatitis. The investigator should determine the tissue establishment's evaluation procedure in those cases when the interviewee responds positively to behavioral risk question(s).

- If the medical director or other responsible person of the firm invalidates risk information, determine if the rationale for accepting a donor in spite of the initial disqualifying information is documented, and evaluate whether or not the decision is contrary to the requirements of 21 CFR 1270. For example, a generic history of hepatitis of an unspecified type disqualifies the donor. If the medical director later receives documentation that positively establishes that the prospective donor had hepatitis A, and not hepatitis B or hepatitis C (or some other yet-to-be-characterized blood borne chronic hepatitis), then the medical director may declare the donor to be suitable to donate tissues for transplantation. (Documentation that the donor had hepatitis A would include, **from the time of the episode**, a positive anti-HAV test result and/or medical records establishing the clinical diagnosis of hepatitis A. A current anti-HAV positive test result doesn't prove that the past episode of clinical hepatitis was hepatitis A.)

- There is no provision in 21 CFR 1270 which allows the medical director to release unsuitable tissue solely on the basis of their authority or position as medical director.
- e. Corneal retrieval may be performed under state and territorial legislative consent laws that do not require family consent. In these cases, a donor medical history interview is *not* required, and the procurer needs to (1) review the records which are available at the time of corneal procurement and (2) conduct a physical assessment of the donor. Corneal tissue procured under legislative consent shall be documented as such in the summary of records. However, this exception does not apply when tissues other than corneas (e.g., sclera or bone) are procured from the same donor and by the same procurer. Determine if the State in which the firm is physically located has a law which allows corneal retrieval without obtaining consent from next of kin.
- FDA's July 1997 "Guidance for Industry: Screening and Testing of Donors of Human Tissue Intended for Transplantation" contains a list of physical signs that should be included in the firm's physical assessment to determine if the donor exhibits signs of HIV or hepatitis, or of high risk behavior.
- f. If the tissue establishment becomes aware of additional donor information indicative of risk factors for, or clinical evidence of HIV or hepatitis, then the tissue from that donor is considered not suitable for transplantation.

#### 4. Standard Operating Procedures

21 CFR 1270.31 requires each tissue establishment to prepare and follow written procedures for:

- (a) infectious disease testing of donors;
- (b) screening of donors;
- (c) quarantining of tissue; and
- (d) prevention of infectious disease contamination or cross-contamination during processing.

These written procedures must be readily available to personnel in the area where the procedures are performed. Any tissue establishment may use current standard written procedures such as those in a technical manual prepared by another firm or organization, provided the procedures are consistent with and at least as stringent as the requirements specified in 21 CFR 1270.

*Validation and Prevention of Infectious Disease Contamination or Cross-Contamination During Processing*

According to 1270.31(d), tissue establishments are required to have data available that demonstrate the effectiveness of the procedures to prevent infectious disease contamination and cross-contamination during processing. Such data may be obtained by conducting challenges with indicator organisms to determine the effectiveness of the processing procedures, or by conducting literature searches [as 1270.31(e) allows] to demonstrate the effectiveness in eliminating organisms of concern during processing (e.g., EPA-approved chemical sterilants for lab surfaces). Procedures used in processing human tissues and in cleaning between products must be written and the processing establishment must document that they actually follow the procedures.

Determine the firm's system for preventing cross-contamination between those tissues deemed suitable, those deemed unsuitable, and those for which no donor suitability determination has yet been made. (Questions about the adequacy of the firm's activities should be directed to CBER/OCBQ/Program Surveillance Branch, see Part VI.)

To address industry concerns forwarded to FDA regarding the adequacy of an establishment's validation procedures, CBER developed a guidance document, "Guidance for Industry: Validation of Procedures for Processing of Human Tissues Intended for Transplantation", dated March 2002, which has been posted on CBER's website [[www.fda.gov/cber/gdlns/tissval.htm](http://www.fda.gov/cber/gdlns/tissval.htm)]. This guidance provides tissue establishments with a more detailed explanation of the intent of 1270.31(d) and describes some options firms may consider for achieving compliance.

## 5. Records

All human tissue shall be quarantined until the following criteria for donor suitability are satisfied:

- (1) All infectious disease testing under section 1270.21 has been completed, reviewed by the responsible person, and found to be negative; and
- (2) donor screening has been completed, reviewed by the responsible person and determined to assure freedom from risk factors for, and clinical evidence of HIV infection, hepatitis B, and hepatitis C.

Human tissue must either be in quarantine or accompanied by records indicating that the donor was identified, tested, and screened in accordance with the requirements in 21 CFR 1270.21 and determined to be suitable to donate tissue for transplantation.

**NOTE:** If the records are in a foreign language, then in addition to the original records, or copies of them, the tissue must also be accompanied by a translation into English and a statement of authenticity by the translator that specifically identifies the translated documents.

Any firm that generates records used in determining the suitability of the donor shall retain those records and make them available for authorized inspection or upon request by FDA. Human tissue that is to be processed or shipped prior to the determination of donor suitability must be under quarantine, accompanied by records identifying the donor and identifying the tissue as not determined to be suitable for transplantation.

The firm making the donor suitability determination shall retain all of the testing and screening records, or true copies of such records, which were reviewed in making the determination, and shall make these records available for authorized inspection or upon request from FDA. Human tissue found suitable for transplantation must be accompanied by a complete summary of records, or copies of the original records, documenting that all infectious disease testing and screening has been completed, reviewed by the responsible person, and that the donor has been determined to be suitable for transplantation.

FDA accepts completed summaries of such records as long as the summary contains the identity of the testing laboratory, the listing and interpretation of all required infectious disease tests, a listing of the documents reviewed as part of the relevant medical records, and the name of the person or establishment determining the suitability of the human tissue for transplantation. Many human tissue establishments utilize their package insert to contain their summary of records information.

All the records required under 21 CFR 1270 must be maintained for at least 10 years beyond the date of transplantation, if known, distribution, disposition, or expiration, of the tissue, whichever is latest. The investigator may review and copy any records required to be maintained pursuant to 21 CFR 1270.

## 6. Electronic Recordkeeping and Electronic Signatures

21 CFR Part 11 describes the technical and procedural requirements that any FDA regulated firm, including a human tissue establishment, must meet if it chooses to maintain records electronically and/or use electronic signatures. Inspect the firm's system: (1) to ensure that accurate, complete, and legible copies of electronic records are available for review, and (2) to determine how the tissue establishment hold its employees accountable and responsible for actions taken under their electronic signatures.

A more detailed evaluation may be warranted if the investigator initially finds that the tissue establishment's electronic records and/or electronic signatures may not be trustworthy and reliable, or that the electronic recordkeeping system(s) precludes a meaningful FDA inspection.

Districts should consult a Center compliance officer to assess the need for more detailed Part 11 coverage. See Compliance Policy Guide, Section 160.850.

## 7. Registration

On January 8, 2001, FDA issued a final rule to require human tissues establishments to register and list their products with the Agency. The rule also amended the registration and listing regulations that currently apply to human tissues regulated as drugs, devices, and/or biological products. The effective dates of the registration and listing regulation are staggered depending on the type of human tissue products and HCT/P's an establishment is manufacturing.

### Establishments required to register and submit product lists beginning April 4, 2001

Establishments that engage in the recovery, screening, testing, processing, storage, or distribution of human tissue intended for transplantation currently regulated under section 361 of the PHS Act and 21 CFR 1270 are required to register with FDA and list their HCT/P's. New establishments are required to register and list their HCT/P's within 5 days after beginning operations defined in 1270.3(e). Presently, this includes establishments manufacturing HCT/P's that meet the definitions in 1270.3(j) and 1271.3(d)(1).

### Establishments required to register and submit product lists beginning January 21, 2004

Manufacturers of all other HCT/P's (e.g., reproductive cells and tissue, hematopoietic stem cells, and tissues and cells regulated as devices, drugs and/or biological products) as defined 1271.3(d)(2) are to begin registering with FDA and listing their HCT/P's on January 21, 2004.

### Establishments exempt from registration and product listing at this time

Tissue establishments that meet any exception under 1271.15 are exempt from the registration and listing requirements at this time. An establishment that manufactures a HCT/P that does not meet the criteria set out in 1271.10 or qualify for exemption under 1271.15 will have its products regulated as drugs, devices or biological products under the FD&C Act and/or section 351 of the PHS Act, and will be subject to applicable regulations.

Establishments that are manufacturing HCT/P's for research purposes only or for study under an IND do not need to register.

B. IMPORTS

If the firm has received foreign tissue or solicitations to purchase foreign tissue, determine if the foreign suppliers are registered with FDA. The list of registered firms is available at <http://www.fda.gov/cber/tissue/hctregistabl.htm>. If the firm is not shown on the website, contact the CBER Tissue Registration Monitor (see CBER Contacts in Part VI) to confirm their registration status.

Any foreign supplier offering tissue to U.S. firms but not registered with FDA should be reported by e-mail or telephone to DFI so the supplier may be contacted and apprized of the registration requirement if they intend to do business with U.S. tissue establishments. Once registered, foreign firm(s) can be added to the OEI. Imported human tissue is subject to the same requirements as domestically procured tissue.

While the imported human tissue is being held in import status, the documentation accompanying the tissue should be evaluated by the district's import staff to determine its adequacy. Refer to Import Alert #57-08, "Human Tissue Intended for Transplantation," for more detailed instructions. While the records are being reviewed, the tissue (especially if perishable) can be transported under quarantine to the consignee and held under appropriate storage conditions until a decision is made regarding the suitability of the tissue/adequacy of the records. If imported tissue is found to be in violation of 21 CFR 1270, the district may allow voluntary corrective action or may issue an Order for Retention, Recall and/or Destruction (Refer to RPM Chapter 5).

If tissue is imported under quarantine only to undergo processing and then be returned to its country of origin with no distribution in the U.S., screening and testing for communicable viruses is not required. However, the tissue must be quarantined, accompanied by records assuring identification of the donor, and indicating that the tissue has not been determined to be suitable for transplantation. The processor must follow the requirements in 1270.31(d) to insure there is no infectious disease contamination or cross-contamination between the quarantined/untested foreign tissue and tissue that is intended for domestic distribution.

Human tissues imported for purposes other than transplantation, such as diagnostic testing, non-clinical research, educational use, or for further processing into another FDA regulated product, are not subject to 21 CFR 1270, nor are they considered to be biological products subject to licensure in accordance with Section 351(a) of the PHS Act, nor are these products regulated as drugs or devices as defined in Section 201(g) and (h), respectively, of the FD&C Act. Therefore,



FDA will not object to the entry or exportation of tissue not intended for transplantation for the stated purpose of either diagnostic testing, non-clinical research, or educational use. If districts are made aware of these shipments, they may want to monitor these shipments, e.g., intermittently check on the actual destination/disposition of shipments, to assure there is no diversion for transplantation.

Human tissues identified for further manufacturing into a device or device component are the responsibility of CDRH. Districts encountering such tissues should contact CDRH for guidance.

C. REPORTING

Report *briefly* on all major systems covered during the inspection, whether in compliance or not (e.g., does the firm have validated procedures to prevent infectious disease contamination or cross-contamination during processing).

**PART IV -- ANALYTICAL**

Collection of physical samples is not planned under this Compliance Program.

Should a district wish to collect physical samples, prior to their collection, the district should contact the Division of Inspections and Surveillance (HFM-650) to discuss the usefulness of collecting a physical vs. a documentary sample, and for guidance and instructions regarding sample size, mode of shipment, method of packaging for shipment, and the laboratory to which the sample should be submitted.

**IMPORTANT:** Prior to the submission of physical samples to CBER laboratories, the district must notify the CBER Sample Custodian (301-594-6517) of the date and method of shipment.

Results of analyses will be forwarded to the appropriate District Compliance staff. Questions concerning analytical results should be directed to HFM-650. Copies of collection reports for physical samples should be submitted to HFM-650.

**PART V -- REGULATORY/ADMINISTRATIVE STRATEGY**

Deviations from 21 CFR1270 and/or subparts A and B of 1271 should be brought to the firm's attention on a Form-483, Inspectional Observations, at the conclusion of the inspection.

Violative conditions must be promptly evaluated during and following an inspection to ensure the continued safety of human tissue intended for transplantation. The strategy and actions outlined below are those believed to be most appropriate and expeditious when donor suitability or tissue safety is in question.

If unsuitable tissue is encountered and the district intends to recommend a compliance action, the EIR must include the labeling associated with the final products and documentation of the extent of processing of the tissue, so that a determination can be made that the proper regulations are being applied. The level of manipulation of the tissue and the intended use of the tissue (as reflected in the labeling) play a role in determining how the product is regulated.

The provisions of 21 CFR 1270 and subparts A and B of 1271 are to be applied to all human tissue intended for transplantation regardless of its origin. Human tissue procured from foreign sources is subject to the same requirements as tissue recovered domestically. Import Alert #57-08 provides investigators with guidance for import coverage regarding human tissue intended for transplantation.

The district may provide a tissue establishment the opportunity to voluntarily correct violative practices through issuance of a Opportunity for Voluntary Corrective Action letter prior to considering an administrative or regulatory remedy such as a Warning Letter or an Order for Retention, Recall, and Destruction. However, voluntary action should be considered only in situations where (1) non-compliant practices do not present an imminent hazard or danger to health, or (2) where a significant pattern of non-compliance does not exist.

Submit recommendations for administrative or regulatory action to the Division of Case Management (HFM-610).

To take action, the district's evidence must include documentation of jurisdiction over the individual/firm and product and the regulatory provisions that have been violated. Jurisdiction is demonstrated by documenting that the individual or organization is a regulated entity and that they are procuring, processing, storing, and/or distributing human tissue intended for transplantation.

Before judicial intervention is attempted, the district should first consider issuance of a Warning Letter or, if appropriate, the administrative remedies of tissue retention, recall, and/or destruction outlined in the regulation, 21 CFR 1270.43. FDA may order that the tissue be recalled and destroyed, and that persons in possession of the tissue retain it until it is recalled by the distributor, destroyed, or disposed of as agreed to by FDA, or the safety of the tissue is confirmed. FDA is also authorized to take possession of and/or destroy the violative tissue; however, this should only be done as a last resort.

**NOTE:** There is no direct reference authority for the issuance of Warning Letters or Orders for Retention, Recall, and Destruction. Opportunity for Voluntary Corrective Action letters may be issued without CBER review and concurrence, though discussion with HFM-610 is suggested.

**NOTE:** Depending on the circumstances, there may be situations where both a Warning Letter and an Order, or both an Opportunity for Voluntary Corrective Action Letter and an Order are warranted. It is not anticipated that FDA will issue an Opportunity for Voluntary Corrective Action Letter and a Warning Letter for the same inspection.

#### A. OPPORTUNITY FOR VOLUNTARY CORRECTIVE ACTION

Occasionally, unsuitable tissue exists in inventory at the tissue bank or has been distributed, but violative conditions leading to the existence of the unsuitable tissue **do not appear to suggest system related problems**. In these instances, districts should consider allowing tissue establishments the opportunity to voluntarily bring the violative tissue into compliance or to destroy it through issuance of an Opportunity for Voluntary Corrective Action letter before recommending an Order for Retention, Recall, and/or Destruction. Unsuitable tissues to be included in an Opportunity for Voluntary Corrective Action letter are those that, if left uncorrected by the firm, would likely be considered for incorporation into an Order for Retention, Recall, and/or Destruction (see part V, section C for criteria for an Order).

Refer to RPM Chapter 5, Subchapter "Order for Retention, Recall, and/or Destruction of Human Tissue," of the RPM for procedural instructions for issuance of an Opportunity for Voluntary Corrective Action letter.

B. WARNING LETTER

A Warning Letter (WL) may be issued to a tissue establishment when FDA considers one or more of its products and/or practices to be in violation of 21 CFR 1270. The issuance of a WL may be appropriate in cases **when systems problems or procedures need to be brought into compliance** with 21 CFR 1270. The violations cited should be appropriate for the issuance of a WL (e.g. significant deficiencies, recurring or continuing deficiencies, or effect on product safety). FDA's policy concerning the issues must be clear. There should be reasonable expectation that correction will be prompt, and there must be sufficient documentation of the violations. In addition, the WL can include notification to the firm of the need to bring unsuitable tissue into compliance (e.g., product quarantine or notification to consignees), if necessary. A WL also establishes prior notice if further legal action becomes necessary.

The WL recommendation along with a draft WL should be forwarded to the Division of Case Management (HFM-610) within 15 working days of the inspection. If the Division of Case Management and the Office of Chief Counsel (OCC) concur with the recommendation, the WL should be issued as soon as possible.

Examples of deviations from 21 CFR 1270 that could be used for the basis of a Warning Letter, if well documented and representative of a continued pattern of operation, include but are not limited to, the following:

1. Testing

A. Testing for anti-HIV-1, anti-HIV-2, HBsAg, or anti-HCV not routinely performed in accordance with the manufacturers' instructions, e.g., use of outdated reagents, failure to use the proper number of positive and negative controls, and failure to dispense the appropriate volumes of test sample and reagents [21 CFR 1270.21(a)]

B. Testing for anti-HIV-1, anti-HIV-2, HBsAg, or anti-HCV not routinely performed at a CLIA certified laboratory [21 CFR 1270.21(c)]

C. Tissue from a donor whose specimen tested repeatedly reactive on a screening test for anti-HIV-1, anti-HIV-2, HBsAg, or anti-HCV was inappropriately determined to be suitable for transplantation [21 CFR 1270.21(h)].

D. Failure to use FDA-approved HIV and hepatitis test kits for cadaveric specimens when available.

E. Use of an unacceptable plasma dilution algorithm/procedure.

2. Donor Screening

Tissue inappropriately deemed suitable for transplantation when the donor's suitability determination for freedom of risk factors for and clinical evidence of hepatitis B, hepatitis C, and HIV infection did not include all available relevant medical records or documented risk factors for or clinical evidence of hepatitis B, hepatitis C, and HIV infection, e.g., non-medical injection of drugs in the preceding five years; sex in exchange for money or drugs in the preceding five years; blue or purple spots on the skin or mucous membranes typical of Kaposi's sarcoma; unexplained yellow jaundice or hepatomegaly [21 CFR 1270.21(f)].

3. Written Procedures

A. Written procedures for significant steps in the infectious disease testing process do not conform to the manufacturers' instructions [21 CFR 1270.31(a)]

B. No written procedure for all significant steps for obtaining, reviewing, and assessing the relevant medical records of donors [21 CFR 1270.31(b)]

Refer to RPM Chapter 4, Subchapter Warning Letters, for procedural instructions for issuance of a Warning Letter.

C. ORDER FOR RETENTION, RECALL AND/OR DESTRUCTION

The option to order retention, recall and/or destruction of unsuitable tissue is available to FDA under 21 CFR 1270.43 and is used when the Agency determines that it must act **to prevent distribution of violative tissue and to ensure the continued safety of the tissue supply.**

FDA's policy concerning the violations must be clear, and the deviations must be well documented. Situations where there are significant concerns regarding the source of the tissue, the adequacy of the screening and/or testing, or a failure of the tissue establishment to fulfill stated commitments to gain control over or properly determine suitability of non-compliant tissue may result in the issuance of an Order for Retention, Recall and/or Destruction (Order).

Recommendations for issuance of an Order should be submitted to the Division of Case Management (HFM-610).

The regulations permit FDA and the tissue firm to develop a strategy regarding the disposal of unsuitable tissue. Within the provisions of the Order, the tissue establishment is permitted to implement corrective action to bring the violative tissue into compliance. If the tissue can be reconditioned to become suitable for transplantation as a result of these corrective actions, the district may authorize release of the tissue for distribution. Unless an alternate resolution can be found, the violative tissue must be recalled and/or destroyed within 5 working days of receipt of the Order.

The regulations, according to 21 CFR 1270.43(e), also permit tissue establishments/individuals to request a Part 16 hearing regarding FDA's orders for retention, recall and/or destruction within 5 working days of receipt of the Order. If a hearing is requested, destruction of the violative tissue is placed in abeyance. However, the provisions of the Order regarding recall and retention of violative tissue remain in place and are not impacted by the hearing request.

Timeliness is very important in the decision to issue an Order, otherwise the perceived seriousness of a firm's non-compliance may be diminished. The recommendation to issue an Order along with a draft copy of the Order should be forwarded to the Division of Case Management (HFM-610) within 15 working days of the inspection. If the Division of Case Management and OCC concur with the recommendation, the Order should be issued as soon as possible.

Examples of deviations from 21 CFR 1270 that could be used for the basis of a Order for Retention, Recall and/or Destruction, if well documented, include but are not limited to, the following:

1. Tissue that tested repeatedly reactive for anti-HIV-1, anti-HIV-2, HBsAg, or anti-HCV has been distributed. **NOTE:** There may be rare circumstances when additional information may lead FDA to view the original, repeatedly reactive result as a probable false positive and, therefore, an Order may not be appropriate.
2. Tissue untested for anti-HIV-1, anti-HIV-2, HBsAg, or anti-HCV has been distributed.
3. Tissue procured from a donor who exhibited clear clinical evidence of or risk factors for hepatitis B, hepatitis C, or HIV infection has been distributed.  
Refer to RPM Chapter 5, Subchapter "Orders for Retention, Recall and/or Destruction of Human Tissue," for procedural instructions for issuance of an Order.

D. PROSECUTION

It is Agency policy to consider prosecution of individuals when there is documented evidence of fraud, gross violations, a hazard to health and/or continuing significant violations. With the exception of prosecutions involving gross, flagrant, or intentional violations, fraud, or danger to health, the criminal charges should show a continuous or repeated course of violative conduct. This may consist of counts from two or more inspections, or counts from separate violative shipments at different points in time.

Section 368 of the PHS Act is the applicable statute when pursuing prosecution for violating regulations promulgated under Section 361 of the PHS Act.

Specific guidance and models for prosecutions have not yet been established, and districts should refer to RPM Chapter 6, Subchapter "Prosecutions," for general procedural instructions concerning prosecution.



## **PART VI -- REFERENCES AND PROGRAM CONTACTS**

### **REFERENCES**

Public Health Service (PHS) Act, Sections 361 and 368 [42 U.S.C. 264 and 271]

Title 21, Code of Federal Regulations (21 CFR), Parts 16, 1270 and subparts A & B of Part 1271  
[<http://first.fda.gov/fedreg/html/links.htm>]

Import Alert #57-08, "Human Tissue Intended For Transplantation," April 13, 1998  
[[www.fda.gov/cber/tissue/docs.htm](http://www.fda.gov/cber/tissue/docs.htm)]

December 14, 1993 Interim Rule: Human Tissue Intended For Transplantation [58 FR 65514]  
[[www.fda.gov/cber/tissue/docs.htm](http://www.fda.gov/cber/tissue/docs.htm)]

July 29, 1997 Final Rule: Human Tissue Intended For Transplantation [62 FR 40429]  
[[www.fda.gov/cber/genadmin/ftissue.txt](http://www.fda.gov/cber/genadmin/ftissue.txt)]

March 4, 1997 Proposed Approach To Regulation of Cellular and Tissue-Based Products [62 FR 9721] [[www.fda.gov/cber/gdlns/CELLTISSUE.txt](http://www.fda.gov/cber/gdlns/CELLTISSUE.txt)]

September 30, 1999 Proposed Rule: Suitability Determination for Donors of Human Cellular and Tissue Based Products [64 FR 52696] [[www.fda.gov/cber/rules/suitdonor.txt](http://www.fda.gov/cber/rules/suitdonor.txt)]

January 8, 2001 Proposed Rule: Current Good Manufacturing Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement [66 FR 1508]  
[[www.fda.gov/cber/rules/gtp010801pr.htm](http://www.fda.gov/cber/rules/gtp010801pr.htm)]

January 19, 2001 Final Rule: Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing [66FR 5447]  
[[www.fda.gov/cber/rules/ftisreg011901.htm](http://www.fda.gov/cber/rules/ftisreg011901.htm)]

Alphabetical List of Registered [Tissue] Establishments  
[[www.fda.gov/cber/tissue/hctrege establ.htm](http://www.fda.gov/cber/tissue/hctrege establ.htm)]

Investigations Operations Manual (IOM)

Regulatory Procedures Manual (RPM): Chapter 4 Advisory Actions (Warning Letters and Untitled Letters); Chapter 5 Administrative Actions (Order for Retention, Recall and/or Destruction of Human Tissue); Chapter 6 Judicial Actions; Chapter 7 Recall Procedures (Mandatory Recalls of Human Tissue Intended for Transplantation); Chapter 9, Subchapter - Importation of Biological Products.

Standards for Tissue Banking, April 2002, American Association of Tissue Banks, 1350 Beverly Road, Suite 22A, McLean, VA 22101

Eye Bank Association of America Medical Standards, December 2001, Eye Bank Association of America, 1001 Connecticut Ave., NW, Suite 601, Washington, DC 20036

#### MEMORANDA AND GUIDELINES

“Guidance for Screening and Testing of Donors of Human Tissue Intended for Transplantation” (July 1997) [[www.fda.gov/cber/gdlns/tissue2.txt](http://www.fda.gov/cber/gdlns/tissue2.txt)]

“Guidance for Industry: Validation of Procedures for Processing of Human Tissues Intended for Transplantation” (March 2002) [[www.fda.gov/cber/gdlns/tissval.htm](http://www.fda.gov/cber/gdlns/tissval.htm)]

“Guidance for Industry: Availability of Licensed Donor Screening Tests Labeled for Use with Cadaveric Blood Specimens” (June 2000) [[www.fda.gov/cber/gdlns/cadbld.htm](http://www.fda.gov/cber/gdlns/cadbld.htm)]

“Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P’s)” (May 2002) distinguishes between tissues regulated by CDRH as devices and tissues regulated by CBER. [See ATTACHMENT B]

Guide to Inspection of Infectious Disease Marker Testing Facilities (June 1996)

PHS/CDC "Guidelines for Preventing Transmission of Human Immunodeficiency Virus Through Transplantation of Human Tissue and Organs" MMWR 1994;43/RR-8; 1-17

PHS "Inter-Agency Guidelines for Screening Donors of Blood, Plasma, Organs, Tissues, and Semen for Evidence of Hepatitis B and Hepatitis C" MMWR 1991;40/RR-4; 1-17

Draft Guidance for Industry: Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) - 6/14/2002  
<http://www.fda.gov/cber/gdlns/cjdvcjd0602.htm>

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH PROGRAM CONTACTS

**Division of Inspections & Surveillance, HFM-650** 301-827-6220 fax 301-827-6748

**Program Surveillance Branch**

Function: Tissue, blood and blood products safety, surveillance and compliance  
Provide inspectional guidance regarding blood/blood products and tissues  
Review of FDA-483s  
Jerome Davis, Branch Chief  
[davis@cber.FDA.gov]  
Lois Simmons, CSO  
Juliaette Johnson, CSO

**Division of Case Management, HFM-610** 301-827-6201 fax 301-594-0940

**Blood and Tissue Compliance Branch**

Function: Process recommendations for administrative and legal action  
Orders for Retention, Recall, and/or Destruction,  
Warning Letters, Injunctions, Prosecutions  
Kathleen Lewis, Branch Chief  
[lewiska@cber.FDA.gov]  
Contact any CSO in DCM

**Biological Drug and Device Compliance Branch**

Function: Provide guidance regarding imports and exports of products that fall under  
CBER's purview, including human tissues.  
Robert Sausville, Branch Chief  
[sausville@cber.FDA.gov]

**Office of Cells, Tissues and Gene Therapy**

**Division of Human Tissues, HFM-770** 301-827-0078 fax 301-827-2844

Function: Regulatory oversight of the tissue transplant industry  
Ruth Solomon, MD, Acting Director  
[solomonr@cber.FDA.gov]  
Melissa Greenwald, MD  
Antonio Pereira, MD  
Martha Wells, M.P.H.  
Rosemarie Wiseman, Tissue Registration Monitor 301-827-6176

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ORA CONTACT

**ORA/ORO/DEIO/HFC-130** 301-827-5662 fax 301-827-6685  
Christine Twohy, CSO  
[ctwohy@ora.FDA.gov]

**PART VII - CBER RESPONSIBILITIES**

Periodic evaluation of this Compliance Program, with conclusions and recommendations, will be coordinated and/or prepared by CBER in conjunction with ORA's Field Biologics Program Committee.

7341.002      **ATTACHMENT A**

**CMS CENTER FOR MEDICARE & MEDICAID SERVICES & STATE OPERATIONS REGIONAL  
OFFICE STAFF**

Internet address: <http://www.cms.hcfa.gov/>

Region I (CT,ME,MA,NH,RI,VT)  
DHHS/CMS/CMSO  
Boston Regional Office  
J.F.K. Fed. Building  
Boston, MA 02203-0003  
Phone: (617) 565-9156  
Charles Reynold, Lab Consultant

Region II (NJ,NY,PR,VI)  
DHHS/CMS/CMSO  
\*New York Regional Office  
26 Federal Plaza, Rm. 3800  
New York, NY 10278-0063  
Phone: (212) 264-9127/3850  
Camelita Ragaza, Lab. Consultant  
Joseph Gialdella, Lab Consultant

Region III (DE,DC,PA,MD,VA,WV)  
DHHS/CMS/CMSO  
Philadelphia Regional Office  
The Public Ledger Bldg., 2nd Floor  
150 S Independence Mall West  
Philadelphia, PA 19106-3499  
Phone: (215) 861-4289/4187/4285  
Eric Arendash, Lab Consultant  
Ben Snyder, Lab Consultant  
Kim Weaver, Lab Consultant

Region IV (AL,FL,GA,KY,MS,NC,SC,TN)  
DHHS/CMS/CMSO  
Atlanta Regional Office  
Atlanta Federal Center  
61 Forsyth Street, Suite 4T20  
Atlanta, GA 30303-8909  
Phone: (404) 562-7443/7455/7450  
Gwendolyn Williams, Lab Consultant  
Regina Holmes, Lab Consultant  
Martha Personett, Lab Consultant

Region VI (AR,LA,NM,OK,TX)  
DHHS/CMS/CMSO  
Dallas Regional Office  
302 Young, Rm. 833  
Dallas, TX 75202-4348  
Phone: (214) 767-4414/4400  
Sandra Pearson, Lab Consultant  
Greg Soccio, Lab Consultant

Region VII (IA,KS,MO,NE)  
DHHS/CMS/CMSO  
Kansas City Regional Office  
601 East 12<sup>th</sup> Street, Rm. 242  
Kansas City, MO 64406-2808  
Phone: (816) 426-3184  
Diana Fairbanks, Lab Consultant  
Reggie Haug, Lab Consultant

Region VII (CO,MT,ND,SD,YT,WY)  
DHHS/CMS/CMSO  
Denver Regional Office  
Federal Office Bldg., 5<sup>th</sup> Floor  
1600 Broadway, Ste. 700  
Denver, CO 80202  
Phone: (303) 844-4722  
Karlou Mattern, Lab Consultant

Region IX (AZ,CA,HI,NV,ASamoa,Guam)  
DHHS/CMS/CMSO  
San Francisco Regional Office  
75 Hawthorne Street, 4<sup>th</sup> Floor  
San Francisco, CA 94105-3903  
Phone: (415) 744-3729/3738/3709/3728  
Ester-Marie Carmichael, Lab Consultant  
Gary Yamamoto, Lab Consultant  
Holly Stern, Lab Consultant  
Cornell Prodan, Lab Consultant

Region V (IL,IN,MI,MN,OH,WI)  
Chicago Regional Office  
233 N. Michigan Ave., Ste 600  
Chicago, IL 60601-5519  
Phone: (312) 886-4392/3595  
Elizabeth Clay, Lab Consultant  
Bonnie Scimera, Lab Consultant

Region X (AK,ID,OR,WA)  
DHHS/CMS/CMSO  
Seattle Regional Office  
2201 6th Avenue RX-42  
Seattle, WA 98121  
Phone: (206) 615-2325/2710  
Fran Lehr, Lab Consultant  
Edwin Prichard, Lab Consultant

Central Office, CMS  
MSO, SCG, Mail Stop S2-12-25  
7500 Security Boulevard  
Baltimore, MD 21244-1850  
Judy Yost, Director, Division of Laboratories and Acute Care Services  
Phone: (410) 786-3531  
Clarissa Weaver, Health Insurance Specialist, (410)786-3406 E-mail:cweaver@cms.hhs.gov

#### FDA/ CMS REGIONAL CONTACTS

Northeast Region	Sylvia Craven, Supervisory Investigator New England District Office 781-279-1787
Central Region PA,NJ,MD,DE,VA, WV,OH, and KY	Susan Setterburg, Regional Food & Drug Director Central Region 215-597-8058
IL,MN,WI,ND,SD, IN and MI	Andrew Bonanno, Dep Regional Food & Drug Dir Central Region 312-353-9400 x 120
Southeast Region	Dawn Todd-Murrell, Director, Investigations Branch Atlanta District Office 404-253-1180
Southwest Region	Dale L.Graham, Superviory Investigator Dallas District Office/Houston Resident Post 713-802-9095 x 131

Pacific Region  
WA,OR,ID,MT, and  
AK

David A. Pettenski, Supervisory Investigator  
Seattle District Office  
425-483-4912

CA,AZ

Timothy LaFave, Investigator  
Los Angeles District Office  
949-798-7693

HI,NV,AmSamoa, and  
Guam

Sue Nelson, Supervisory Investigator  
San Francisco District Office  
916-930-3674



## **FDA REGULATION OF HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS (HCT/P's)**

This document is intended as an inspectional tool to assist FDA Investigators and Compliance Officers in distinguishing between the human cells, tissues, and cellular and tissue-based products (HCT/P's) that are regulated by the Center for Devices and Radiological Health (CDRH) as medical devices and those that are regulated by the Center for Biologics Evaluation and Research (CBER). A section is also included for combination products.

### **I. CBER**

#### **HCT/P's Regulated under 21 CFR 1271.3(d)(1) and Section 361 of the PHS Act**

These HCT/P's generally are regulated solely as "361 products" because they ordinarily meet all of the criteria in 21 CFR 1271.10(a):

- BONE (including DEMINERALIZED BONE, or containing a sterilizing, preserving, or storage agent, and THREADED/MACHINED CORTICAL BONE DOWELS)
- LIGAMENTS
- TENDONS
- FASCIA
- CARTILAGE
- OCULAR TISSUES (CORNEAS & SCLERA)
- SKIN
- VASCULAR GRAFTS (e.g., SAPHENOUS VEINS), except umbilical cord veins
- PERICARDIUM
- AMNIOTIC MEMBRANE **when used alone/without added cells for ocular repair**

**HUMAN SOMATIC CELL THERAPY AND GENE THERAPY PRODUCTS**  
**Regulated under Sec. 351 of the PHS Act and/or the FD&C Act**

This grouping includes products that FDA has determined do not meet all of the criteria in 21 CFR 1271.10(a) and are regulated as drugs and/or biological products.

- CULTURED CARTILAGE CELLS
- CULTURED NERVE CELLS
- LYMPHOCYTE IMMUNE THERAPY ([www.fda.gov/cber/ltr/lit013002.htm](http://www.fda.gov/cber/ltr/lit013002.htm))
- GENE THERAPY PRODUCTS
- HUMAN CLONING ([www.fda.gov/cber/ltr/aacclone.htm](http://www.fda.gov/cber/ltr/aacclone.htm))
- HUMAN CELLS USED IN THERAPY INVOLVING THE TRANSFER OF GENETIC MATERIAL (cell nuclei, oocyte nuclei, mitochondrial genetic material in ooplasm, genetic material contained in a genetic vector) ([www.fda.gov/cber/ltr/cytotrans070601.htm](http://www.fda.gov/cber/ltr/cytotrans070601.htm))

**II. CDRH**

**DEVICES COMPOSED OF HUMAN TISSUES Regulated under the FD&C Act and device regulations, 21 CFR 820**

- HEART VALVES
- DURA MATER
- CORNEAL LENTICULES
- PRESERVED UMBILICAL CORD VEIN GRAFTS
- HUMAN COLLAGEN
- FEMORAL VEINS INTENDED AS A-V SHUNTS

**III. COMBINATION PRODUCTS**

- DEMINERALIZED BONE combined with HANDLING AGENTS (glycerol, sodium hyaluronate, calcium sulfate, gelatin, collagen) – are regulated as DEVICES
- BONE-SUTURE-TENDON ALLOGRAFTS – regulated as DEVICES

- CULTURED CELLS (fibroblasts/keratinocytes/nerve/ligament/bone marrow) on SYNTHETIC MEMBRANES or combined with COLLAGEN are regulated as DEVICES or BIOLOGICAL PRODUCTS (these products are currently under review and may be regulated by CBER under either the device authorities or section 351 of the PHS Act)
- ENCAPSULATED PANCREATIC ISLET CELLS are regulated as BIOLOGICS

This document, revised in May 2002, is subject to further change as the regulation of tissues by FDA continues to evolve.

CBER Contact: Jerome Davis (HFM-650) 301-827-6220  
CDRH Contact: Gene Berk (HFZ-404) 301-594-1190 ext. 132

### **TISSUE REFERENCE GROUP**

To help answer questions about how a particular human tissue product will be regulated by FDA, the agency developed the Tissue Reference Group (TRG). If an establishment is not sure how its human tissue product(s) may be regulated, it should contact the TRG.

The TRG provides a single reference point and makes recommendations to the Center Directors regarding regulation of specific human tissue products, e.g., regulation solely under section 361 of the PHS Act or additionally under the Food, Drug and Cosmetic Act, and/or section 351 of the PHS Act. The TRG is composed of: three representatives from the Center for Biologics Evaluation and Research (CBER), including the product jurisdictional officer; three representatives from the Center for Devices and Radiological Health (CDRH), including the product jurisdictional officer; and a liaison from the Agency's Ombudsman's Office (OO), a non-voting member. Other FDA staff attend the TRG meetings as needed to discuss issues related to products in their area of expertise. Further information about the TRG can be found on CBER's website at <http://www.fda.gov/cber/tissue/trg.htm>.

In some cases, a product will fall under the jurisdiction of more than one FDA component, e.g., a combination device and biological product. Where the FDA component with primary jurisdiction is unclear or in dispute, a sponsor may request designation from the product jurisdiction officer, who is the FDA Ombudsman, as detailed in 21 CFR part 3. In addition, the Ombudsman can assist in resolving disputes with FDA that may arise from decisions made by the Center Directors regarding the regulation of HCT/P's, after consideration of TRG recommendations, as described above.